# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)

Pavlakis, et al.

Serial No.

TBA

Examiner: TBA

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Art Unit: TBA

For

METHOD OF ELIMINATING INHIBITORY/

INSTABILITY REGIONS OF mRNA

# PRELIMINARY AMENDMENT PURSUANT TO 37 CFR 1.111 AMENDING CLAIMS, UPDATING INFORMATION CONCERNING RELATED APPLICATIONS, AND ADDING SEQUENCE LISTING

COMMISSIONER FOR PATENTS Washington, D.C. 20231

Sir:

Prior to examining the above-captioned application, please make the following amendments. This amendment is submitted in order to add claims corresponding to claims in U.S. Patent No. 6,114,148, update the information in the specification concerning related applications, and to add the sequence listing. A copy of each of U.S. Patent No. 6,114,148 and related U.S. Patent No. 5,786,464 and U.S. Patent No. 5,795,737 is submitted herewith.

Also submitted herewith are pages 87-120 of the sequence listing containing the sequences (Exhibit A), a Letter Requesting Transfer of Computer Readable Form of Sequence Listing Filed in Parent Application Ser. No. 09/678,437, filed October 2, 2000 (which was filed in Parent Application Ser. No. 08/850,049, filed May 2, 1997, and then transferred to Parent Application Ser. No. 09/414,117, filed October 8, 1999 and then transferred to Parent Application

Ser. No. 09/678,437, filed October 2, 2000) (Exhibit B), and a statement under 37 C.F.R. § 1.821 (f) or 1.825(b) or (d) that the paper sequence listing and the computer readable form containing the sequence listing submitted herewith are identical (Exhibit C).

In addition, a copy of the Supplemental Combined Declaration and Power of Attorney, Associate Power of Attorney, and Change of Correspondence Address forms which were filed in application U.S. Serial No. 08/050,478 on March 25, 1998 (and also in application U.S. Serial No. 08/850,049 on the same date) are attached hereto (Exhibit D).

#### **AMENDMENT**

Please amend the application as follows:

In the specification:

On page 1, please delete the sentence concerning the priority applications, which is immediately below the title, and insert the following in its place:

-- This application is a continuation of 09/678,437 filed October 2, 2000, which is a continuation of U.S. Serial No. 09/414,117, filed October 8, 1999, which is a continuation of U.S. Serial No. 08/850,049, filed May 2, 1997 (now U.S. Patent 5,965,726), which is a continuation of U.S. Serial No. 08/050,478, filed October 26, 1994 (now U.S. Patent 5,972,596), which is in turn a continuation of the National Stage under 35 U.S.C. §371 of PCT/US93/02908, filed March 29, 1993, which is in turn a continuation-in-part of U.S. Serial No. 07/858,747, filed March 27, 1992 (now U.S. Patent 6,174,666 B1). The disclosures of each of these applications is hereby incorporated by reference. --

After page 86 and before the claims, please insert pages 87 to 120 of the sequence listing attached hereto as Exhibit A.

In the claims:

Please add the following new claims:

- 46. (New) A synthetic gene encoding a protein normally expressed in an eukaryotic cell wherein at least one rarely-used or less preferred codon in a natural gene encoding said protein has been replaced by a preferred codon encoding the same amino acid, said synthetic gene expressing said protein at a level which is higher than that expressed by said natural gene in an in vitro mammalian cell culture system under identical conditions.
  - 47. (New) An expression vector comprising the synthetic gene of claim 46.
  - 48. (New) A mammalian cell comprising the synthetic gene of claim 47.
- 49. (New) A method for preparing a synthetic gene encoding a protein normally expressed by mammalian cells, comprising identifying rarely-used and less-preferred codons in the natural gene encoding said protein and replacing one or more of said rarely-used or less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon, so that a synthetic gene is prepared.

### REMARKS

# 1. The Pending Claims

Claims 3-5, 21, 23-24, 30 and 34-45 were canceled in the application fee transmittal paper filed together herewith, leaving original claims 1-2, 6-20, 22, 25-29, and 31-33 pending in the application. New claims 46-49 are being added. After entry of the amendment, claims 1-2, 6-20, 22, 25-29, 31-33 and 46-49 will be pending.

### 2. Amendments

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

# a. The specification

The specification has been amended to update the status of the related applications. The specification has been amended to include a sequence listing containing nucleotide and amino acid sequences referred to elsewhere in the specification.

# b. The claims

New claims 46-49 have been added. Pursuant to 37 C.F.R. § 1.607(c), Applicants identify these claims as corresponding to claims 1, 13, 14 and 18 of U.S. Patent No. 6,114,148, respectively, as demonstrated by the chart below:

Seed U.S. 6,114,148	New Claims 46-49
(issued 9/5/00)	
1. A synthetic gene encoding a protein	46. A synthetic gene encoding a protein
normally expressed in an eukaryotic cell	normally expressed in an eukaryotic cell
wherein at least one nonpreferred or less	wherein at least one rarely-used or less
preferred codon in a natural gene encoding said	preferred codon in a natural gene encoding
protein has been replaced by a preferred codon	said protein has been replaced by a preferred
encoding the same amino acid, said synthetic	codon encoding the same amino acid, said
gene expressing said protein at a level which is	synthetic gene expressing said protein at a
at least 110% of that expressed by said natural	level which is higher than that expressed by
gene in an in vitro mammalian cell culture	said natural gene in an in vitro mammalian
system under identical conditions.	cell culture system under identical conditions.
13. An expression vector comprising the	47. An expression vector comprising the
synthetic gene of claim 1.	synthetic gene of claim 46.
14. A mammalian cell which harbors the	48. A mammalian cell comprising the
synthetic gene of claim 1.	synthetic gene of claim 46.
18. A method for preparing a synthetic gene	49. A method for preparing a synthetic gene
encoding a protein normally expressed by	encoding a protein normally expressed by
mammalian cells, comprising identifying non-	mammalian cells, comprising identifying
preferred and less-preferred codons in the	rarely-used and less-preferred codons in the
natural gene encoding said protein and replacing	natural gene encoding said protein and
one or more of said non-preferred and less-	replacing one or more of said rarely-used or
preferred codons with a preferred codon	less-preferred codons with a preferred codon
encoding the same amino acid as the replaced	encoding the same amino acid as the replaced
codon, so that a synthetic gene is prepared.	codon, so that a synthetic gene is prepared.

See also, Seed U.S. Patent Nos. 5,786,464 and 5,795,737 for related claims.

#### Claim 46 is directed to

A synthetic gene encoding a protein normally expressed in an eukaryotic cell wherein at least one rarely-used or less preferred codon in a natural gene encoding said protein has been replaced by a preferred codon encoding the same amino acid, said synthetic gene expressing said protein at a level which is higher than that expressed by said natural gene in an in vitro mammalian cell culture system under identical conditions.

Claims 47 and 48 are directed to an expression vector and mammalian cell,

respectively, comprising the synthetic gene of claim 46. Claim 49 is directed to

a method for preparing a synthetic gene encoding a protein normally expressed by mammalian cells, comprising identifying rarely-used and less-preferred codons in the natural gene encoding said protein and replacing one or more of said rarely-used or less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon, so that a synthetic gene is prepared.

Support for new claims 73-76 can be found throughout the specification. See, e.g., p. 9, lines 20-23, for support for synthetic genes and expression vectors and host cells containing these genes. See also, e.g., p. 39, line 32 to p. 40, line 6. Support for genes encoding a protein normally expressed in an eukaryotic cell can be found, e.g., on p. 22, lines 27-35; p. 23, lines 3-6; and p. 40, lines 28-32, which describe examples of genes, including the eukaryotic "cellular" genes listed therein. Support for mutating a gene by replacing rarely-used or less-preferred codons with preferred codons encoding the same amino acid can be found, e.g., at p. 20, lines 15-17; p. 20, lines 31-33; p. 21, lines 17-19; p. 33, lines 22-24 and 27-29; p. 36, line 26 to p. 37, line 7; and Example 1.

Support for expressing the protein from the mutated gene at a level which is higher than that expressed by the natural gene in vitro in mammalian cell culture under identical conditions is found, e.g., on p. 26, line 7; p. 41, lines 6-9; p. 40, lines 14-23; p. 14, lines 17-27; and in Example 1 and Figure 2.

Applicants respectfully submit that the above amendments do not constitute new matter and respectfully request entry thereof.

# **CONCLUSION**

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: August 31, 2001

Registration No. 34,398

Mailing Address: MORGAN & FINNEGAN, L.L.P. 345 Park Avenue New York, New York 10154 (212) 758-4800 Telephone (212) 751-6849 Facsimile

#### VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification (on page 1):

-- This application is a continuation of 09/678,437 filed October 2, 2000, which is a continuation of U.S. Serial No. 09/414,117, filed October 8, 1999, which is a continuation of U.S. Serial No. 08/850,049, filed May 2, 1997 (now U.S. Patent 5,965,726), which is a continuation of U.S. Serial No. 08/050,478, filed October 26, 1994 (now U.S. Patent 5,972,596), which is in turn a continuation of the National Stage under 35 U.S.C. §371 of PCT/US93/02908, filed March 29, 1993, which is in turn a continuation-in-part of U.S. Serial No. 07/858,747, filed March 27, 1992 (now U.S. Patent 6,174,666 B1). The disclosures of each of these applications is hereby incorporated by reference. -- [This application is a continuation-in-part of U.S. Serial No. 07/858,747, filed March 27, 1992.]

#### In the claims:

- 46. (New) A synthetic gene encoding a protein normally expressed in an eukaryotic cell wherein at least one rarely-used or less preferred codon in a natural gene encoding said protein has been replaced by a preferred codon encoding the same amino acid, said synthetic gene expressing said protein at a level which is higher than that expressed by said natural gene in an in vitro mammalian cell culture system under identical conditions.
  - 47. (New) An expression vector comprising the synthetic gene of claim 46.
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- 49. (New) A method for preparing a synthetic gene encoding a protein normally expressed by mammalian cells, comprising identifying rarely-used and less-preferred codons in the natural gene encoding said protein and replacing one or more of said rarely-used or less-

preferred codons with a preferred codon encoding the same amino acid as the replaced codon, so that a synthetic gene is prepared.